IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Eugene R. Cooper et al.
Title:	NANOPARTICULATE MELOXICAM FORMULATIONS
Appl. No.:	10/784,900
Filing Date:	2/24/2004
Examiner:	Tran, Susan T.
Art Unit:	1615
Confirmation Number:	1015

DECLARATION UNDER 37 C.F.R. §1.132

The undersigned, Gary Liversidge, hereby declares as follows:

I. Background of Gary Liversidge

1. I received my Ph.D. in 1981 from the University of Nottingham, England, in Pharmaceutical Chemistry. I have been working in the field of nanoparticulate drug technology since 1987, when I joined Eastman Pharmaceuticals.

2. Through a series of business transactions, Eastman Pharmaceuticals became Sterling Winthrop Pharmaceuticals Research Division, which became known as NanoSystems. This business is currently known as the Elan Drug Technologies (EDT) business division of Elan Corp. PLC. Intellectual property developed at EDT is owned by Elan Pharma International Ltd. (an affiliate of Elan Corp., PLC), which is the assignee of the above-referenced patent application.

3. Currently I am Vice-President and Chief Technology Officer of EDT, with offices at 3500 Horizon Drive, King of Prussia, PA 19406.

II. Final Office Action

4. I have thoroughly reviewed the cited references, PCT Publication No. WO 99/09988 by Struengmann et al. ("Struengmann") and PCT Publication No. WO 93/25190 by Liversidge et al. ("Liversidge"), as well as the final Office Action dated February 15, 2011.

5. It is my understanding that the Examiner asserts that it would have been obvious to modify Struengmann's micronized meloxicam in view of the method of Liversidge to obtain the claimed invention. *See* final Office Action, pages 3 and 4.

III. Teachings of Struengmann

6. Struengmann describes improving the solubility of meloxicam, thereby improving bioavailability, by mixing meloxicam with one or more additives, such as surfactants, co-solvents, hydrotropic agents, alkalizing agents, cyclodextrins, hydrocolloids, and pharmaceutically acceptable polymers. *See* the abstract, and page 3, 3rd full paragraph.

7. Other than a general statement that "the solubility and bioavailability of meloxicam can be improved by micronisation of the substance" in the presence of a co-solvent or a hydrotropic agent (Struengmann, page 3, last paragraph, and page 4, first paragraph), Struengmann does not have any disclosure regarding the particle size of meloxicam, as the Examiner acknowledges in the final Office Action, at page 3, lines 14-15.

8. The exemplary co-solvents and hydrotropic agents disclosed by Struengmann in the context of micronisation do not include polyvinylpyrrolidone or sodium deoxycholate, which are the surface stabilizers required by the claimed invention.

9. Although Struengmann lists polyvinylpyrrolidone in the laundry list of suitable additives in the paragraph bridging pages 4 and 5, Struengmann fails to teach or suggest that polyvinylpyrrolidone is preferred to other additives. None of the working examples of

Struengmann in the context of micronization demonstrate that meloxicam is formulated in the presence of polyvinylpyrrolidone. Rather, Struengmann teaches that cyclodextrin is preferred, especially when used in combination with other additives, for "further improvement of solubility and bioavailability." *See* page 4, 5th paragraph. Moreover, the working examples demonstrate many formulations of meloxicam and cyclodextrin. *See* Examples IV/1 through IV/12.

10. In summary, Struengmann does not teach the particle size of meloxicam or one of the surface stabilizers of the claimed invention, sodium deoxycholate. Moreover, Struengmann fails to suggest selection of the other surface stabilizer of the claimed invention, polyvinylpyrrolidone, from a laundry list of additives. Finally, Struengmann fails to teach or suggest any correlation between particle size reduction of meloxicam and improved solubility of meloxicam.

IV. Teaching of Liversidge

11. Liversidge relates to nanoparticulate nonsteroidal anti-inflammatory drug (NSAID) compositions. *See* the abstract. Liversidge further discloses a number of exemplary NSAIDs, including the subgenus of oxicams "such as piroxicam, sudoxicam, isoxicam and tenoxicam." *See* page 4, lines 16-36. Liversidge does not explicitly teach meloxicam.

12. Liversidge discloses a laundry list of surface stabilizers, including polyvinylpyrrolidone. *See* page 5, line 10, through page 6, line 24. However, Liversidge fails to disclose sodium deoxycholate as an exemplified surface stabilizer.

V. Superior Stability of the Claimed Compositions

13. The claimed meloxicam compositions demonstrate superior stability. A number of nanoparticulate meloxicam formulations were tested for stability under different storage temperatures, 5°C, 25°C, and 40°C, for a period of two months. It was unexpected that the

claimed nanoparticulate meloxicam compositions exhibited superior stability even at lower or elevated temperature for an extended period of time, as detailed in Table 1 below.

Table 1

	Storage time	Condition	Dmean	D50	D90
Formulation	Days	°C	nm	nm	nm
2.5% meloxicam, 0.5% PVP K17	30	25	157	95	334
	30	40	295	259	476
2.5% meloxicam, 0.5% PVP K17, 0.25% NaDOC	60	5	99	89	121
	60	25	101	90	127
	60	40	106	91	145
2.5% meloxicam, 0.25% PVP K17, 0.25% Tween 80	29	5	273	256	417
	29	25	468	446	710
	29	40	585	566	858
2.5% meloxicam, 0.5% PVP K12, 0.25% NaDOC	62	5	102	89	130
	62	25	104	91	137
	62	40	106	91	148
2.5% meloxicam, 0.5% Tween 20, 0.5% Span 20	29	5	113	89	225
	29	25	451	425	696
	29	40	548	537	825
2.3% meloxicam, 0.5% PVP K17, 2.3% PEG 400, 0.23% NaDOC	0	NA	123	105	214
2.5% meloxicam, 0.5% PVP K17, 0.25% NaDOC, 200 mM Sodium Phosphate pH 9	7	5	139		
2.5% meloxicam, 0.5% PVP K17, 0.125% NaDOC, 125 mM Sodium Phosphate pH 7.5	14	5	139		
2.3% meloxicam, 0.46% PVP K17, 0.23% NaDOC, 50 mM Sodium Phosphate pH 6	7	5	102		
2.7% meloxicam, 0.54% PVP K17, 200 mM Sodium Phosphate pH 9	14	5	164		
2.5% meloxicam, 0.5% PVP K17, 0.08% NaDOC, 0.1M Potassium Phosphate pH 7.5	0	5	115		
3.4% meloxicam, 0.68% PVP K17, 0.23% NaDOC, 0.68% Tween 80, 100 mM Sodium Phosphate pH 8	0	5	220		

VI. Exemplary nanoparticulate meloxicam compositions of the claimed invention achieved improved pharmacokinetic profiles in comparison to a commercial formulation

14. An *in vivo* clinical trial was conducted to compare the bioavailability of the claimed meloxicam compositions with that exhibited by the commercial, microparticulate meloxicam composition, MOBIC® tablet.

15. Exemplary nanoparticulate meloxicam compositions of the claimed invention, in both liquid dosage form and in solid dosage form, along with the commercial MOBIC® tablet, were orally administered to Beagle dogs. Following administration, the pharmacokinetic parameters (C_{max}, T_{max} and AUC) were measured from the blood samples of the Beagle dogs. The nanoparticulate meloxicam formulations of the claimed invention achieved ***significantly improved*** pharmacokinetic profiles *in vivo* in comparison to the conventional, microparticulate meloxicam composition, MOBIC®. More specifically, the improved C_{max}, T_{max} and AUC are summarized in Table 2 below.

Table 2

Formulation	Particle Size	C_{max}		T_{max}		AUC	
		C_{max} (μg/mL)	improvement relative to MOBIC®	T_{max} (hours)	improvement relative to MOBIC®	AUC	improvement relative to MOBIC®
Liquid dispersion comprising nanoparticulate meloxicam and Poloxamer 407	111 nm	3.499	126%	0.750	22%	118.225	118%
Lyophilized wafer comprising nanoparticulate meloxicam, polyvinylpyrrolidone and docusate sodium	101 nm	3.420	124%	1.292	38%	106.642	107%
commercial MOBIC® tablet	<10 μm	2.768	--	3.375	--	99.870	--

16. An exemplary injectable nanoparticulate meloxicam formulation comprising polyvinylpyrrolidone and sodium deoxycholate as the surface stabilizers was tested in human patients in comparison to the commercially available, microparticulate meloxicam tablet, MOBIC®. Due to the large particle size, MOBIC® is formulated into oral dosage forms rather than injectable forms. The nanoparticulate meloxicam formulations of the claimed invention consistently achieved significantly increased blood plasma drug concentration in all patient groups as represented by AUC_{last} and AUC_{inf} in Table 3 below.

Table 3

Meloxicam Dosage (mg)	AUC (ng*hr/mL)	Nanoparticulate meloxicam injectable formulation	MOBIC® tablet	% of increase of AUC by nanoparticulate formulation
Cohort (15 mg)	Last	46094.8 (14565.8)	42949.2 (11662.8)	107%
	Inf.	57314.4 (27233.2)	53988.8 (23207.7)	106%
Cohort 2 (30 mg)	Last	92575.9 (18456.0)	88340.6 (16547.1)	105%
	Inf.	107508.7 (34443.0)	104400.0 (30656.2)	103%
Cohort 3 (60 mg)	Last	156042.6 (24041.4)	146677.3 (21925.3)	106%
	Inf.	171229.0 (34439.1)	163854.7 (32916.7)	105%

CONCLUSION

17. The data described herein demonstrate the superior physical stability and *in vivo* bioavailability represented by improved pharmacokinetic profiles of the nanoparticulate meloxicam compositions of the claimed invention.

18. I declare that the statements made herein of my knowledge are true and all statements on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therein.

Gary Liversidge

5/16/11

Date